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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Brian Seed et al.	Art Unit:	1617
Serial No.:	09/735,024	Examiner:	S. Hui
Filed:	December 12, 2000	Customer No.:	21559
Title:	METHODS AND COMPOSITIONS FOR THE RAPID AND ENDURING RELIEF OF INADEQUATE MYOCARDIAL INFARCTION		

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APPELLANTS' BRIEF ON APPEAL SUBMITTED PURSUANT TO 37 C.F.R. § 1.192

In support of Appellants' Notice of Appeal that was filed in connection with the above-captioned case on March 11, 2003, and with reference to the final Office Action that was mailed in this case on November 5, 2002, submitted herewith in triplicate is Appellants' brief on appeal.

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TABLE OF PROSECUTION DOCUMENTS PRESENTED IN APPEAL

Patent Application, filed December 12, 2000, and assigned U.S. Serial Number 09/735,024

Office Action mailed on February 26, 2002

Reply mailed on July 25, 2002

Submission of abstracts from Schmidt et al. (*Blood Coagul. Fibrinolysis* 1993, 4:173-175), Yanagita et al. (*Clin. Ther.* 1994, 16:200-208), and Bisgaier (*Lipids* 1994, 29:811-818) on July 25, 2002

Office Action mailed on November 5, 2002

Reply mailed on March 5, 2003

Submission of Daoud et al. Arch. Pathol. Lab. Med. 1976, 100:372-379 and abstracts from Chiari et al. (Pharmacol. Res. 1996, 33:181-189) and Nicholson et al. (Lipids 1995, 30:771-774) on March 5, 2003

Notice of Appeal mailed on March 5, 2003 (received on March 11, 2003)

Advisory Action mailed on April 1, 2003

Real Party in Interest

The real parties in interest in this case are the inventors, Brian Seed and John C. Seed.

Related Appeals and Interferences

There are no pending appeals or interferences related to this case.

Status of Claims

Claims 55-71 are pending. Claims 1-54 have been cancelled. Claims 55-60, 62, 63, 65-68, 70, and 71 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 55-71 stand further rejected under 35 U.S.C. § 103(a). Claims 55-71 are on appeal.

Status of Amendments

All amendments have been entered and are reflected in the appended claims.

Summary of the Invention

In general, Appellants' invention features a method for reducing a coronary artery stenosis by at least 20% that involves the administration of a combination of (a) a composition comprising eicosapentaeneoic acid or docosahexaeneoic acid and (b) a cholesterol synthesis or transfer inhibitor, in combination with limiting fat or cholesterol intake, whereby a serum LDL concentration of less than or equal to 70 mg/dl is achieved

(page 3, line 10 to page 4, line 21 and page 6, lines 4-11). The method may further include administration of niacin, aspirin, a bile acid sequestrant, or buspirone (page 4, lines 10-15).

Issues

Two issues are presented on appeal.[1] The first issue is whether the Examiner erred in rejecting claims 55-60, 62, 63, 65-68, 70, and 71 under 35 U.S.C. § 112, first paragraph as being based on a non-enabling disclosure. And the second issue is whether the Examiner erred in rejecting claims 55-71 under 35 U.S.C. § 103(a) as being obvious over Sassen et al. (Cardiovasc. Drugs Ther. 1994, 8:179-191; hereafter "Sassen"), Vane et al. (Circulation, 1991; 84:2588-2590; hereafter "Vane"), Lee et al. (Am. J. Cardiol. 1994, 73:1037-1040; hereafter "Lee"), Watts et al. (Lancet 1992, 339:563-569; hereafter "Watts"), and Demopulos et al. (U.S. Patent No. 5,800,385; hereafter "Demopulos").

Grouping of Claims

For the purpose of this appeal, claims 55-60, 62, 63, 65-68, 70, and 71 stand or fall together for the rejection under 35 U.S.C. § 112, first paragraph. Claims 55-71 do not stand or fall together for the rejection under 35 U.S.C. § 103(a). Claims 55-57, 59-65,

[1] Claims 55-71 were also rejected under 35 U.S.C. § 112, second paragraph in the final Office Action, but, as the Examiner did not reiterate this rejection in the Advisory Action mailed on April 1, 2003, Appellants assume that this rejection has been withdrawn.

and 67-69 stand together, claims 58 and 66 stand together, and claims 70 and 71 stand together for the reasons discussed below.

Arguments

I. The Present Claims Are Enabled by the Specification

The first issue presented on appeal involves the rejection of claims 55-60, 62, 63, 65-68, 70, and 71 for lack of enablement. These claims are directed to methods of reducing coronary stenosis by 20% and include administration of a cholesterol synthesis or transfer inhibitor, which lowers serum cholesterol. The rejection is based on two grounds. First is the assertion that "[g]iven that ... no common core structural, physical or chemical properties of the cholesterol synthesis inhibitors or cholesterol transfer inhibitors have been provided, the skilled artisan would be required to conduct undue experimentation in order to select compounds that will be useful in the practice of the instant invention" (Paper 10, page 3). The second basis for the rejection is an assertion that the specification fails "to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation" (Paper 10, page 3). According to the Office's reasoning, one skilled in the art would have to conduct undue experimentation initially to assay for compounds that are cholesterol synthesis or transfer inhibitors and then to identify which of these compounds work in the claimed methods. Appellants assert that these bases for rejection are improper for the instant invention.

As stated in M.P.E.P. § 2164.01, the standard for enablement is that the application, as filed, must contain sufficient information regarding the subject matter of the claims to enable one skilled in the pertinent art to make and use the claimed invention. The skilled artisan in the instant case is a physician experienced with treating patients with heart disease. Because such physicians receive many years of specialized training, the level of knowledge on available pharmaceutical agents and the level of skill for such a physician in selecting appropriate pharmaceutical agents is high.

Appellants assert that the specification provides ample disclosure for a physician skilled in treating heart disease to identify compounds that are cholesterol synthesis or transfer inhibitors. In contrast to the apparent belief of the Office, physicians do not develop new drugs; they prescribe drugs already on the market or administer experimental drugs with known properties. Based on the disclosed desired effect, i.e., lowering cholesterol, and its general mechanism, i.e., inhibiting cholesterol synthesis or esterification (specification page 7, lines 3-9), a physician would be able to determine whether a given compound should be used in the method of the invention. It is not necessary for the physician to understand the precise mechanism of action of the cholesterol synthesis or transfer inhibitor, or, for that matter, for the physician to determine whether the reduction in cholesterol level occurs by inhibition of cholesterol synthesis or transfer. Nor is it necessary for the physician to screen thousands of compounds for new cholesterol drugs. Rather, the physician merely needs to employ one

of the many compounds known and available for lowering the cholesterol level of a patient.

In addition to the understanding of cholesterol-lowering drugs in the art is the disclosure in Appellants' specification, for example, on page 7, lines 7-9, where several cholesterol synthesis or transfer inhibitors are disclosed. Moreover, Appellants have submitted abstracts that illustrate the prevalence of these compounds in the art (Schmidt et al. (*Blood Coagul. Fibrinolysis* 1993, 4:173-175), Yanagita et al. (*Clin. Ther.* 1994, 16:200-208), Bisgaier (*Lipids* 1994, 29:811-818), Chiari et al. (Pharmacol. Res. 1996, 33:181-189), and Nicholson et al. (Lipids 1995, 30:771-774)), providing further guidance on the selection of a cholesterol synthesis or transfer inhibitor.

The present disclosure is also not required to provide common core structural, physical, or chemical properties of cholesterol-lowering compounds because physicians do not select drugs based on these properties. One skilled in the pertinent art would be able to select cholesterol-lowering compounds based on the information provided in the specification and the level of skill in the art. No experimentation is thus required in order to select a cholesterol synthesis or transfer inhibitor because a physician employing the instant methods needs only to select from the many available drugs that inhibit cholesterol synthesis or transfer.

Furthermore, a physician would be able to identify cholesterol synthesis or transfer inhibitors that are operable in the present invention. There is no reason to believe that any given compound that lowers cholesterol levels (whether by inhibition of cholesterol

synthesis or transfer) would not be beneficial in the claimed methods. The purpose of the cholesterol synthesis or transfer inhibitor in the claimed methods is to lower cholesterol; therefore, there is a strong presumption that any available cholesterol synthesis or transfer inhibitor would be efficacious in the present methods because it lowers cholesterol. Thus, armed with the knowledge of the type of medication desired, a physician could select an appropriate cholesterol synthesis or transfer inhibitor for use in the claimed methods using only routine practices. No undue experimentation is necessary.

The rejection of claims 55-60, 62, 63, 65-68, 70, and 71 for lack of enablement has been applied in error and should be reversed.

II. Appellants' Claimed Method Is Not Suggested by the Prior Art

To support an obviousness rejection, the Office must put forth a *prima facie* case that meets the legal standard for obviousness found in M.P.E.P. § 2142. This section states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991) (emphasis added).

This summary in the M.P.E.P. is based on Federal Circuit case law. For example, as stated by the Federal Circuit, "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). As the Federal Circuit recently observed:

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. . . . Most if not all inventions arise from a combination of old elements. . . . Thus, every element of a claimed invention may often be found in the prior art. . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. . . . Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000) (citations omitted) (emphasis added).

The evidence of a suggestion, teaching, or motivation to combine "must be clear and particular." *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617. "Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GMBH*, 139 F.3d 877, 881, 45 U.S.P.Q.2d 1977, 1981 (Fed. Cir. 1998). "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617.

Thus, even if the Examiner identifies every element of a claimed invention in the prior art, this alone is insufficient to negate patentability. Otherwise, "rejecting patents

solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457 (Fed. Cir. 1998). To avoid hindsight based on the invention to defeat patentability of the invention, the Federal Circuit requires an Examiner to show a motivation to combine the references that create the case of obviousness. *Id.* That is, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.* (emphasis added).

Recently, in discussing the motivation to combine references the Federal Circuit noted that "[t]he factual inquiry [of] whether to combine references must be thorough and searching." *In re Sang Su Lee,* 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002), *quoting McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-1352, 60 U.S.P.Q.2d 1001, 1008 (Fed. Cir. 2001). Furthermore, "the factual question of motivation [to combine references] is material to patentability, and ...[cannot] be resolved on subjective belief and unknown authority." *Lee*, 277 F.3d at 1344, 61 U.S.P.Q.2d at 1434. Rather, the motivation to combine references "must be based on objective evidence of record." *Lee*, 277 F.3d at 1343, 61 U.S.P.Q.2d at 1433. "This precedent has been reinforced in myriad decisions, and cannot be dispensed with." *Id.*

Furthermore, it is "impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965) (emphasis added).

In applying these legal standards to the present case, it is clear that a *prima facie* case of obviousness has not been established. Claim 55, from which all other claims depend, recites:

> 55. A method for reducing coronary artery stenosis by at least 20% in a mammal comprising the administration to said mammal of a combination of (a) a composition comprising eicosapentaeneoic acid or docosahexaeneoic acid and (b) a cholesterol synthesis or transfer inhibitor, in combination with limiting fat or cholesterol intake, whereby a serum LDL concentration of less than or equal to 70 mg/dl is achieved. (emphasis added)

Thus, the present claims are all directed to methods for reducing established narrowing in coronary arteries using a combination therapy requiring three components: (1) eicosapentaeneoic acid or docosahexaeneoic acid (components of fish oil), (2) a cholesterol synthesis or transfer inhibitor, and (3) limiting fat or cholesterol intake. Claims 58 and 66 further include the administration of aspirin, and claims 70 and 71 further include the administration of buspirone, as components of the method of claim 55.

To support the obviousness rejection, the Office has cited four references, Sassen (Cardiovasc. Drugs Ther. 1994, 8:179-191), Lee (Am. J. Cardiol. 1994, 73:1037-1040), Vane (Circulation, 1991; 84:2588-2590), and Watts (Lancet 1992, 339:563-569) as teaching the three major components of the claimed methods, with Demopulos (U.S.

Patent No. 5,800,385) cited as teaching an additional element in claim 70. These references simply do not provide Appellants' invention. Sassen reviews several studies on the use of fish oil for the prevention and regression of atherosclerosis. Vane discloses the use of aspirin and fish oil for the prevention of thrombosis. Lee discloses the use of pravastatin, niacin, and LDL apheresis for the prevention of restenosis after angioplasty. Watts teaches the use of a controlled diet, with or without administration of cholestyramine, for the regression of atherosclerosis. And Demopulos teaches the use of a solution of various compounds, potentially including buspirone, to inhibit undesirable effects (e.g., pain, inflammation, spasm, and restenosis) of cardiovascular therapeutic and diagnostic procedures.

These references, even in combination, do not provide all of the limitations of the claimed invention, nor do the references provide a suggestion or motivation for their combination. Moreover, the cited references provide no reasonable expectation that such a combination would have led to success. Each of these issues is discussed in more detail below.

A. The References Do Not Teach or Suggest All of the Claim Limitations

Claim 55 and its dependent claims are directed to methods of reducing coronary artery stenosis by 20% by treatment with eicosapentaeneoic acid or docosahexaeneoic acid, a cholesterol synthesis or transfer inhibitor, and limited fat or cholesterol intake. Importantly, the instant methods result in a reduction in stenosis, i.e., the widening of

coronary arteries already occluded, which is entirely distinct from prevention of a recurrence of stenosis after angioplasty (i.e., restenosis). The present methods are therefore analogous to a treatment for healing a wound as opposed to a treatment for preventing an injury. As indicated above, these methods also require the administration of a cholesterol synthesis or transfer inhibitor.

Regarding the patentability of claim 55 and its dependent claims, the Office has cited only one reference, Lee, as disclosing the use of a cholesterol synthesis or transfer inhibitor – the compound pravastatin. As stated above, however, Lee discusses the use of pravastatin as one component of a treatment for the prevention of restenosis, a use different from the claimed reduction of stenosis. Lee fails entirely to disclose that pravastatin is useful for the reduction of stenosis in patients already having occluded coronary arteries. No other reference has been cited for this proposition. Thus, the Office has failed to provide a teaching of one of the three major components of the methods of the instant claims for the reduction of stenosis, and, on this basis alone, the rejection should be reversed.

B. There Is No Motivation to Combine the References

In addition to the above, Appellants further point out that nothing in these references motivates the combination of their various therapeutic agents and behavioral modifications to allow one skilled in the art to arrive at Appellants' invention. As the courts have held, to render a combination obvious, the prior art must do more than

disclose the individual elements; the prior art must suggest the claimed combination as well. M.P.E.P. § 2143.01 states, "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination" (emphasis in original) *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The courts have consistently upheld this standard stating that "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed" (emphasis added). *Kotzab*, 217 F.3d at 1371, 55 USPQ2d at 1317. In addition, "there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant" (emphasis added). *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998).

For example, in the case of *In re Fromson*, 755 F.2d 1549, 225 U.S.P.Q. 26 (Fed. Cir. 1985), the claimed invention was a photographic plate for use in planographic printing. The district court held the patent invalid for obviousness, finding that "the Fromson patent is a combination patent comprised of old elements." The Federal Circuit, while conceding that the prior art disclosed all of the individual elements of the invention, reversed, stating:

> At no point did the court indicate, nor does the record indicate, a basis on which it can be said that the making of that combination would have been obvious when it was made.... The critical inquiry is whether "there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." (emphasis in the original, citing *Lindeman Maschinefabrik GMBH v.*

> *American Hoist & Derrick Co.*, 730 F.2d at 1462, 221 U.S.P.Q. at 488.) Where, as here, nothing of record plainly indicates that it would have been obvious to combine previously separate process steps into one process, it is legal error to conclude that a claim to that process is invalid under § 103.

While the art cited in the present case discloses some of the individual elements of the claimed methods, it does not suggest the making or the desirability of the unique combination of the claimed method for Appellants' particular purpose, as required for a finding of obviousness.

Indeed, the only basis for the combination of the cited art currently made of record is the assertion by the Office, based on *In re Kerkhoven*, 625 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (M.P.E.P. § 2144.06) that "it flows logically to combine or incorporate agents, which are known to be useful individually for treating or preventing restenosis, into a single combination or method useful for the same purpose" (Paper 10, page 11) (emphasis added).

On this issue, Appellants first point out that the purpose alleged by the Office (treating or preventing restenosis) is not the purpose of the instant claims, which is reducing stenosis. Thus, the purported motivation provided by the Office is not sufficient to establish a *prima facie* case of obviousness, as motivation to develop a method for preventing restenosis cannot negate the patentability of Appellants' claims, which are directed to a method of reducing stenosis.

Moreover, the Office likely took this position because the cited references simply do not provide motivation for a combination of the three major components of the instant

claims as a useful treatment for reducing stenosis. In particular, Lee teaches the use of a cholesterol synthesis or transfer inhibitor, but only as one component for preventing restenosis, a different medical problem than that solved by the present invention.

Sassen discusses the use of fish oil, but states that "only a randomized clinical trial ... can reliably answer the question whether fish oil is effective as a non-pharmacological adjuvant in the prevention of restenosis" (page 186, col. 1). Furthermore, Sassen states:

> Maybe it is also time to temper the overrated expectations of the therapeutic effect of n-3 fatty acids. In this respect, it is of interest to note that also the capability of n-3 fatty acid-rich diets to reduce the incidence of ischemic heart disease has been questioned. (emphasis added; page 188)

Sassen goes on to undermine the original basis for considering fish oil as a possible treatment for heart disease, namely questioning whether it is diet consisting mainly of fatty fish or genetics that predispose Eskimos to a low incidence of ischemic heart disease (page 188). Thus, one skilled in the art would not be motivated by reading Sassen to use fish oil in a combination therapy for any ischemic heart condition, since Sassen questions the efficacy and underlying scientific assumptions of the treatment.

The remaining references cited as teaching major components, Watts and Vane, also fail to provide this requisite motivation. Watts is directed to regression of atherosclerosis using diet and cholestyramine only, while Vane, which is directed to anti-thrombotic therapy using fish oil and aspirin, does not discuss coronary narrowing in any context.

These teachings therefore provide no motivation for a combination of Lee with Sassen or Vane discussing fish oil, or Watts discussing diet. Thus, there is no motivation

of record to combine the references that purport to teach even two of the three major components of the instant claims.

Furthermore, Watts teaches away from Appellants' methods by teaching away from combining a low fat diet with a cholesterol-lowering drug for reducing stenosis. Watts teaches a diet-induced 23.3% reduction in stenosis (Table V, page 566) in a small number of cases. However, in similar cases where the patient received controlled diet and a cholesterol lowering drug, the treatment was less efficacious than that observed for diet alone (Table V, page 566). Thus, one reading Watts would not be motivated to combine diet with cholesterol-lowering drugs to reduce stenosis because Watts observed reduced efficacy with such a combination.

In view of the above, Appellants submit that the references fail to provide the necessary motivation for their combination, and the Office has therefore failed to establish a *prima case* of obviousness for claim 55 and its dependent claims. On this basis as well, the rejection of Appellants' claims for obviousness should be reversed.

C. The Prior Art Provides No Reasonable Expectation of Success

For yet a third reason, the obviousness rejection in this case should be reversed – the references cited by the Office provide no reasonable expectation of success. The case law is clear that, for an invention to be obvious, there must be a reasonable expectation of its success. The instant claims are directed to methods for reducing coronary artery

stenosis by at least 20%, and none of the cited references suggests that such a reduction is possible using the instantly claimed method.

As stated above, while Watts teaches a 23.3% reduction in stenosis in limited cases using diet alone, this outcome was lessened in similar cases when diet was combined with a cholesterol-lowering drug. Thus, Watts provides no reasonable expectation for a 20% reduction in stenosis for a method that includes both a controlled diet and cholesterol-lowering drug, as instantly claimed.

Regarding the use of fish oil in reducing atherosclerosis, Sassen reviews four exemplary studies (page 187). Sassen states that, of the four studies on regression of atherosclerosis by treatment with fish oil, a study in pigs and a study in rabbits showed regression, a study in pigs showed no change, and a study in monkeys (the animal model closest to humans) showed atherosclerotic progression (page 187), again forecasting a negative outcome for Appellants' claimed method. Moreover, Sassen states that "the number of animal studies investigating the effects of fish oil on the regression of atherosclerosis is too small to draw any conclusion..." (page 188) (emphasis added).

In dismissing these clear statements in the Sassen reference, the Office asserts that "Sassen ... concludes that fish oil is effective in leading [to] regression in certain kinds of components of atherosclerotic lesions" (Paper 14, page 2). This assertion, however, does not support the Office's position; nor does it contradict Appellants' arguments. While Sassen does state that fish oil lowered the lipid content of atherosclerotic lesions in certain animal studies (page 187), it does not conclude that fish oil is effective in reducing

atherosclerosis (page 188). Sassen therefore fails to provide any reasonable expectation that a treatment for reducing stenosis that included fish oil would be effective at all, much less induce a 20% reduction, as required by claim 55.

In addition, the Office states that "several studies [reviewed in Sassen] have shown that fish oil is effective in regression of human lesions" (Paper 10, page 10). Appellants disagree. This statement is contradicted by the last sentence of Sassen, which states that "no attempts have been made to study the influence of n-3 fatty acids in the regression of human atherosclerosis" (page 188). In addition, the Office's reliance at Paper 10, page 10 on Sassen's statements that "relatively advanced lesions can reduce in size over time" (page 186) is misplaced. As acknowledged by the Office (Paper 14, page 2), those studies (e.g., Daoud et al. Arch. Pathol. Lab. Med. 1976, 100:372-379) are based on treatment methods that do not include fish oil. Thus, this general acknowledgement that an outcome is possible using a method distinct from Appellants' method is not relevant to the present case, as it does not provide a reasonable expectation for the success of Appellants' particular treatment regime. This is especially true here, as the same reference actually calls into doubt the effectiveness of Appellants' claimed methods, as discussed more fully above.

In sum, Appellants submit that nowhere in the cited references is a *prima facie* case of obviousness for the methods of instant claim 55 and its dependent claims established. The references, while providing a list of therapeutics and behavioral

modifications, do not teach the unique combinations of claims 55-71, nor do they provide a motivation to combine the references or a reasonable expectation of their success. The § 103 rejection of claims 55-71 should be reversed.

D. Claims 58, 66, 70, and 71

In addition to the reasons stated above, the rejection of claims 58, 66, 70, and 71 should also be reversed because the Office has failed to cite art that teaches the additional elements of these claims. Claims 58 and 66 are directed to the method of reducing stenosis of claim 55 further including the administration of aspirin, and claims 70 and 71 are directed to the method of reducing stenosis of claim 55 further including the administration of buspirone.

Regarding claims 58 and 66, the Office cites Vane as teaching the administration of aspirin as being useful in vasodilatation and platelet inhibition (Paper 10, page 7), medical disorders distinct from stenosis reduction. In response to Appellants' arguments that Vane does not teach the use of aspirin in a method of reducing stenosis, the Office states:

> Agents causing vasodilatation and [preventing] platelet aggregation would have been reasonably expected to be useful in regression of atherosclerosis due to the role of platelet aggregation in atherogenesis. Moreover, aspirin would dilate the blood vessels, which is considered a direct counter effect of restenosis (narrowing). (Paper 10, pages 10-11)

This statement, however, is without documentary basis. Despite Appellants' request, the Office has failed to supply any evidence of the scientific accuracy of this assertion as

required by M.P.E.P. § 2144.03(c) or any other reference that teaches the use of aspirin to reduce stenosis. For this reason, the rejection of claims 58 and 66 has been maintained in error.

Moreover, there is no motivation to combine Vane with the other references to produce the method of claims 58 and 66. Vane is directed to methods of preventing thrombosis and is the sole cited reference disclosing aspirin. As stated above, the motivation provided by the Office for combining the cited art (the use of the disclosed components in methods for the treatment of restenosis) is in error. Thus, there is no motivation to combine Vane with Watts, Sassen, or Lee. For this reason as well, the rejection of claims 58 and 66 should be reversed.

Regarding claims 70-71, the cited references again do not teach all of the claimed limitations, and there is no motivation to combine the cited references to arrive at Appellants' invention. The Office cites Demopulos as teaching the use of buspirone in a method for reducing restenosis. As stated above, the instant claims are directed to methods of reducing stenosis, and therefore prior art teachings on treatments for restenosis are off point. In addition, Demopulos teaches that buspirone is used for the treatment of inflammation and pain (col. 9, ll. 8-10 and col. 13, ll. 1-10), and not for stenosis. Thus, none of the cited art teaches the use of buspirone in a method for reducing stenosis, as required by claims 70 and 71. The rejection of these claims should be reversed.

Furthermore, there is no motivation to combine buspirone as taught by Demopulos with the major components taught in the other references. As stated above, Demopulos teaches that buspirone is an anti-inflammation/anti-pain agent and is silent with regard to treatments for reducing stenosis. Thus, Demopulos fails to teach that buspirone is appropriate for the treatment of Appellants' coronary disease. Demopulos also discloses numerous agents for treatment of various conditions, and the Office has failed to indicate why one skilled in the art would select buspirone from these agents for inclusion in any method, much less a method of reducing stenosis. There is no motivation of record to support a *prima facie* case of obviousness for claims 70 or 71.

Conclusion

Appellants respectfully request that the rejection of claims 55-71 be reversed. Enclosed is a check for $160.00 in payment of the fee required by 37 C.F.R. § 1.17(c). Also enclosed is a copy of the petition to extend the period for submitting an Appeal Brief for one month, to and including June 11, 2003, submitted in connection with this case. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 28 May 2003

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Appendix of Claims on Appeal

55. A method for reducing coronary artery stenosis by at least 20% in a mammal comprising the administration to said mammal of a combination of (a) a composition comprising eicosapentaeneoic acid or docosahexaeneoic acid and (b) a cholesterol synthesis or transfer inhibitor, in combination with limiting fat or cholesterol intake, whereby a serum LDL concentration of less than or equal to 70 mg/dl is achieved.

56. The method of claim 55, wherein said serum LDL concentration achieved is less than 55 mg/dl.

57. The method of claim 55, wherein said combination further comprises niacin.

58. The method of claim 55, wherein said combination further comprises aspirin.

59. The method of claim 55, wherein said composition comprising eicosapentaeneoic acid or docosahexaeneoic acid is administered at greater than or equal to 5 g/day.

60. The method of claim 55, wherein said composition is a marine lipid.

61. The method of claim 60, wherein said marine lipid is a fish oil.

62. The method of claim 55, wherein said cholesterol synthesis or transfer inhibitor is administered at greater than or equal to 10 mg/day.

63. The method of claim 55, wherein said cholesterol synthesis or transfer inhibitor acts by inhibiting hydroxymethylglutarate (HMG) CoA reductase.

64. The method of claim 55, wherein said cholesterol synthesis or transfer inhibitor is chosen from the group consisting of simvastatin, lovastatin, fluvastatin, and pravastatin.

65. The method of claim 57, wherein said niacin is administered at between 0.5 - 3 g/day.

66. The method of claim 58, wherein said aspirin is administered at greater than or equal to 80 mg/day.

67. The method of claim 55, wherein said method further comprises administering to said mammal a bile acid sequestrant.

68. The method of claim 67, wherein said sequestrant is administered at between 5 - 20 g/day.

69. The method of claim 67, wherein said sequestrant is chosen from cholestyramine or colestipol.

70. The method of claim 55, wherein said method further comprises administering to said mammal buspirone.

71. The method of claim 70, wherein said buspirone is administered at between 10 - 80 mg/day.